

## Deep Insight Section Review

### Insight in inflammation and cancer

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#### Abstract

Inflammation starts whenever antigens trigger molecules and cells of the immune system causing them to move to the affected site. This forms part of the body's response to internal and external environmental stimuli that normally eliminate the offending organism or cells and restore the tissue physiology. We have previously shown that chronic inflammation may lead to prostate carcinogenesis in both animal and human models. Substantial data has shown that over 25% of all cancer cases are related to chronic inflammation, and other types of unresolved inflammatory processes. Further evidence for this relationship is the fact that prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced risk to developing many types of cancers. Here we review current available internationally published papers in view of several reports on inflammation and cancer progression and draw a synthesis to provide a concise insight to the emerging field of inflammation and cancer. In particular, the molecular mechanisms underlying the concept of inflammation-mediated cancer development, progression, invasion and metastasis was discussed in detail. Indeed, we provide details to allow readers understand the very new concept that underpin the dual host-protective and tumor-promoting actions of cancer immunoediting and present substantial scientific data that strongly suggest that inflammatory markers might be potent molecular targets for cancer diagnosis, treatment, monitoring and prevention.

**Keywords:** Inflammation, carcinogenesis, Toll-like receptors (TLR), leukocytes migration, chemokines, metastasis, immunoediting

#### 1. Introduction

The quest for protection is fundamental to living organisms or cells. The innate immune system is evolutionally conserved and is the first line of the defensive mechanisms for protecting the host from invading microbial pathogens. Until recently, innate immunity was considered as being nonspecific immune responses mediated by phagocytotic cells such as macrophages and neutrophils that engulf and lyse microbial pathogens (Medzhitov et al., 1997). Experimental evidence showed that *Drosophila* with mutations in specific genes which result in loss-of-function involving the Toll receptor developed high susceptibility to fungi infection and

defective production of an antifungal peptide; this provided the initial evidence that *Drosophila* expresses a specific receptor responsible for sensing fungi infection (Anderson et al., 1985a; Anderson et al., 1985b; Lemaitre et al., 1996). Currently, human homolog of Toll (hToll) which is also known as Toll-like Receptor (TLR) was identified, which was shown to induce production of inflammatory cytokines and expression of costimulatory molecules (Lemaitre et al., 1996; Roach et al., 2005). More recently, this family of pattern recognition receptors has been shown to play a critical role in the elicitation of procancer and anticancer immune responses (Vacchelli et al., 2013).

	Type of cancer	Inflammatory mediators	Reference
1	Hodgkin lymphoma	Autonomous activation of CD40, Notch and RANK	Thomas et al., 2004
2	Non Hodgkin's Lymphoma; MALT – Lymphoma and Burkitt lymphoma	Reactive oxygen species (ROS) and MAPK mediated NF- $\kappa$ B activation	Zucca et al., 1998
3	Multiple Myeloma	NF- $\kappa$ B induced Bcl-xl overexpression	Escobar-Diaz et al., 2005
4	B-cell derived CLL	Increased activity of NF- $\kappa$ B	Cuni et al., 2004
5	AML	IKK signaling dysregulation	Frelin et al., 2005; Baumgartner et al., 2002
6	CML	Increased intrinsic activity of NF- $\kappa$ B	Thomas et al., 2004; Bueso-Ramos et al., 2004
	Mucosa-associated lymphoid tissue (MALT) lymphomas, chronic lymphocytic leukemia (B-CLL), AML - Acute myeloid leukemia, CML- Chronic myeloid leukemia.		

**Table 1:** showing forms of hematological malignancies and associated inflammatory markers.

Therefore, understanding of this molecular interplay would arouse interest in the development of immunochemotherapeutic regimens for cancer therapy. The question here is why should the process of protection be interred- wound with inflammation? And how does inflammation affect cancer initiation, progression and metastasis and chemoprotection. This review therefore provides an insight into the concept of inflammation and cancer development and highlights the mechanism of inflammation mediated carcinogenesis with a view of creating better understanding that may culminate in developing entirely new ideas for targeted cancer therapy and prevention. We first present an overview of the innate immune signaling and highlight the link between innate immunity and adaptive immunity in health.

## 2. The Toll like signaling

Today, up to 10 different forms of TLR in human and 13 in mice have been identified. The TLR system is known to be the pathogen associated molecular patterns used by the innate immune system to identify specific pathogens, targeting them for destruction (Anderson et al., 1985a; Lemaitre et al., 1996; Vacchelli et al., 2013; Hoshino et al., 1999). For example, LPS (lipopolysaccharide) of Gram-negative bacteria is recognized by TLR4 (hToll) and TLR2, in concert with TLR1 or TLR6, recognizes various bacterial components, including peptidoglycan, lipopeptide and lipoprotein of Gram-positive bacteria and mycoplasma lipopeptide (Hoshino et al., 1999; Jiang et al., 2013). Whenever the TLR have

recognized the specific ligand from the microbial pathogens, it triggers an intracellular signaling pathways that result in the transcription of genes leading to the production of inflammatory cytokines, like type I interferon (IFN) and chemokines (Vacchelli et al., 2013; Jiang et al., 2013). In addition, signaling from TLRs induces the expression of costimulatory molecules on specialized antigen-presenting cells called dendritic cells (DCs). This process, called DC maturation, is essential for the induction of pathogen-specific adaptive immune responses, thus indicating that TLRs link innate and adaptive immunity (Hayashi et al., 2001). Specifically, TLRs activates a common signaling pathway that culminates in activation of NF- $\kappa$ B at the cytoplasm and formation of NF- $\kappa$ B complexes in the nucleus; this process is controlled by the activity of the I $\kappa$ B kinase (IKK) complex, which phosphorylates I $\kappa$ B proteins and bind to target DNA sequences to regulate the expression of genes involved in cytokine and chemokine induction, especially pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-1, IL-6, and IL-12 (Vacchelli et al., 2013; Jiang et al., 2013; Hayashi et al., 2001; Yoon et al., 2012). Association of these inflammatory cytokines and cancer promotion and its prognostic implications are discussed in appropriate paragraphs in this work. In brief, a large body of published work has confirmed the ability of TLR agonists to mediate radio-, chemo- or immunotherapy or therapeutic effects against a variety of tumors, including lymphoma, mastocytoma, glioma, breast carcinoma, thymoma, fibrosarcoma, head and neck

cancer, melanoma, lung cancer, colorectal carcinoma, renal cancer, and ovarian carcinoma (Lu et al., 2012; Garaude et al., 2012; Dewan et al., 2012; Li et al., 2012; Betting et al., 2012; Dovedi et al., 2013; Peng et al., 2013); this indicates that TLRs play striking role in inflammation-mediated carcinogenesis (see table 1). Classic Hodgkin's lymphoma is characterized by Hodgkin and Reed-Sternberg cells and in most cases is derived from germinal-centre B cells. It is generally accepted that infection with Epstein - Barr virus may be associated with the formation of Hodgkin and reed-sternberg cells resulting in Hodgkin lymphoma. However the report of Thomas and colleague (Thomas et al., 2004) suggests that a constitutive activity of NF- $\kappa$ B in Hodgkin lymphoma cells may also be a feature of this form of cancer (Table 1). The author showed that the activity of NF- $\kappa$ B was mediated through CD40, CD30, receptor activator of NF- $\kappa$ B (RANK), and Notch surface molecules following TLR stimulation (Thomas et al., 2004). Today, due to strong link between TLR signaling and cancer progression, three TLR agonists are currently approved by FDA for use in cancer patients: bacillus Calmette-Guérin (BCG, an attenuated strain of *Mycobacterium bovis* initially developed as a vaccine against tuberculosis), which is currently approved for the immunotherapy of in situ bladder carcinoma (Hoffman et al., 2005).

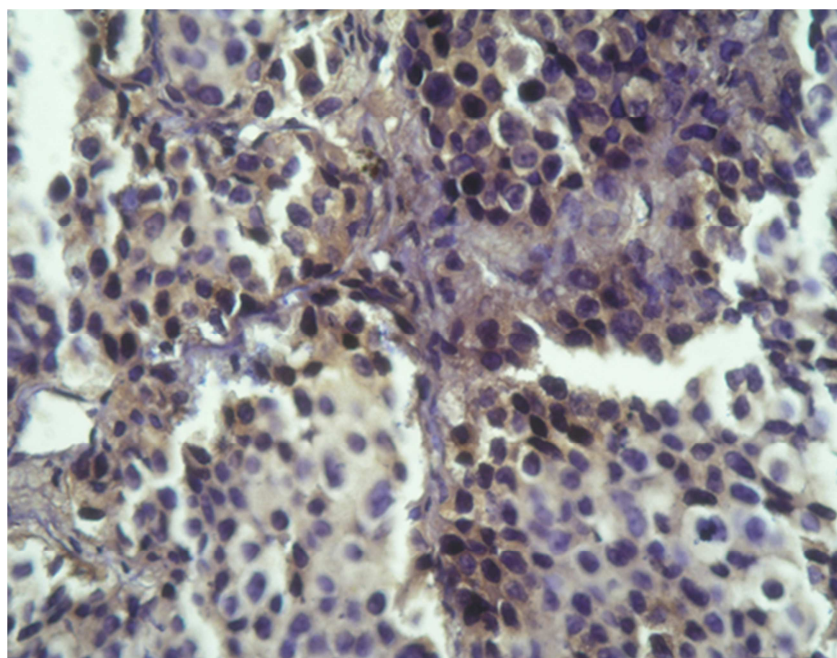
### 3. Inflammatory responses

Inflammation is triggered when epithelial or stoma cells of infected tissue or tissue resident hematopoietic cells such as mast cells or DCs recognizing an inflammatory stimulus and propagating pro-inflammatory signals. These signals lead to the recruitment and activation of effector cells, initially neutrophils and later macrophages and other leukocytes, resulting in the tissue changes characteristic of inflammation - *rubor, calor, dolor*, and *tumor* (redness, heat, pain, and swelling, respectively). This may involve activation of the complement system and generation of molecules including the C5a, which together with C3b and C4a triggers release of some pharmacologically active compounds like histamine from activated mast cells (Roach et al., 2005; Vacchelli et al., 2013; Hoshino et al., 1999). These compounds induce increase in vascular permeability and contraction of the smooth muscles within the local microenvironment (Delves and Roitt, 2000). This may result in tissue damage and release of some molecules from the vascular endothelium which sends signals to cause more cells to pass through the vascular system to the site of the antigen triggering the response (Delves and Roitt, 2000). For example, the neutrophils contain a surface molecular L-seletin while an adhesion

molecule which contains carbohydrate structures including sialyl-lewis located on the surface of the vascular endothelium recognizes and interact with the L-seletin when cell rolls along the vascular bed (Delves and Roitt, 2000). The molecular interaction between the L-seletin and the asialyl-lewis results in activation of the neutrophils and shedding off of the molecular and its replacement with intriguing. The activated neutrophil then pass through the vessel walls to the site of the antigen causing the response (Delves and Roitt, 2000). The process is known as extravasations of leukocytes and it's a known feature of progressive and invasive cancer state (Omabe and Onyekachi, 2013). This event allows different forms of leukocytes and soluble molecules to migrate to the site of the inflammation, making the area to have a number of features in common with the molecular picture of the tumor microenvironment (Omabe and Onyekachi, 2013), figure 1.

### 4. Inflammation and cancer initiation

Evidence from published studies few years back has continued to stimulate a hot debate concerning the role of inflammation and risk of developing malignant cancer disease. Although early study within last decade had observed persistence of inflammatory cells within tumor environment, recently, reports from the authors' laboratory demonstrated a strong link between infection, and conditions associated with inflammatory states (Omabe and Ezeani, 2011); that report pointed out that lack of access to anti inflammatory agents was a key factor that predispose to carcinogenesis in both experimental and clinical studies (Omabe and Ezeani, 2011). Since then there have been more than 100 published articles addressing the role of inflammation and cancer progression. Currently, it is becoming clearer that inflammation may have important role in various forms and stages of tumorigenesis. It was widely accepted that cancer was a genetic disease that run through families; however, available knowledge today suggest that causes of cancer due to genetic inheritance may just be about 10% of all cases - this means that up to 25 - 50% of cancer cases might be as a result of environmental influences which may induce inflammatory states in its molecular pathogenesis (Borroni et al., 2009). Due to lack of full understanding of the parts played by inflammation in carcinogenesis, many authors provide conflicting statistics regarding the actual percent of cancer cases that are due to inflammatory conditions. For example while many suggest that inflammation causes up to 30% of cancer cases, others quote dietary factors to be responsible for 35% cases.



**Figure 1:** showing the tumor microenvironment characterized with alteration in redox signaling and increased level of hypoxia, demonstrated here with increased immunopositivity of Glut-1 antibody (the dark-brown cells) cells with blue staining are non hypoxic. This feature is also found in the tissues with chronic inflammation.

But reports from published studies explained that dietary products may initiate tumorigenesis by first stimulating inflammatory response (Omabe and Ezeani, 2011; Omabe et al., 2012). In addition, tobacco is generally accepted as a known cancer initiator and would be categorized with a significant percentage (Omabe et al., 2012). However emerging evidence now indicates that tobacco smoke also promote carcinogenesis due to its ability to trigger chronic inflammation (Takahashi et al., 2010).

## 5. Inflammation and solid tumor

### 5.1. Leukocyte migration promotes cancer progression

Available evidence suggest that cells found in the microenvironment of tumors often resembles that seen in histology of tissues from chronic inflammation and that increased numbers of neutrophils may be associated with such tumors; these may have implication on prognosis (figure 2). Neutrophil recruitment into tumors appears to be dependent on chemokines that bind to CC, CXCR1 and CXCR2 commonly expressed by neutrophils (figure 2). Thus, chemokine (C-X-C motif) ligand 1 (CXCL1) and its receptor CXCR2 are associated with metastasis potential. Tazzyman and colleagues (Tazzyman et al., 2011) showed that significant reduction in the numbers of infiltrating neutrophils into both in vitro and in vivo tumor models was associated with slower growth of lung tumors. Neutrophil infiltration into A549 tumor spheroids increased their size compared to noninfiltrated spheroids (Tazzyman et al., 2011) The author

showed that neutrophils may contribute to lung tumor growth and that CXCR2 antagonists may be a useful therapeutic agent in the treatment of lung carcinomas (figure 2). In a clinical study that involved the use of quantitative PCR and immunohistochemistry techniques, Cheng and colleagues (Cheng et al., 2011) investigated the functional significance of CXCL1 expression. The author clearly demonstrated that up regulation of CXCL1 correlated significantly with tumor progression, advanced stage of gastric cancer patients, and was one of the independent prognostic factors for patient's survival. Furthermore, cancer cells expressing CXCL1 stably exhibited an increase in cell migration and invasion ability, whereas CXCL1 or CXCR2 depletion significantly reduced the migration and invasion ability of each cell line (Cheng et al., 2011). In addition, by selectively targeting the inflammatory marker CXCR2/CXCR1 with orally active small-molecule inhibitors, an aggressive skin cancer showed significant ( $P < 0.05$ ) decreases in tumor cell proliferation and micro vessel density in tumors. Moreover, further experiments in that study suggested another significant increase in melanoma cell apoptosis compared with the controls (Singh et al., 2009). Another study which also clearly demonstrated that CXCR2 was protumorigenic chemokine receptor, that directs recruitment of tumor-promoting leukocytes into tissues during tumor-inducing and tumor-driven inflammation. Jamieson and colleagues (Jamieson et al., 2012), showed that blockade of CXCR2 profoundly suppressed inflammation-driven tumorigenesis in



skin and intestine as well as spontaneous adenocarcinoma formation even in a model of invasive intestinal adenocarcinoma (Jamieson et al., 2012) see figure 2.

Further experimental evidence showed that CXCR2 deficiency was associated with profound suppression inflammation-driven tumorigenesis in skin and intestine as well as spontaneous adenocarcinoma formation in a model of invasive intestinal adenocarcinoma and that CXCR2 inhibition reduced tumorigenesis in mice (Jamieson et al., 2012). It is thought that CXCR2 influences tumor through multiple mechanisms and might promote tumor development (Jamieson et al., 2012). In addition, sufficient leukocyte populations were found in human intestinal adenomas, suggesting that inflammation by migratory leukocytes may induce tumor development (Jamieson et al., 2012).

## 5.2. Macrophage infiltration and cancer

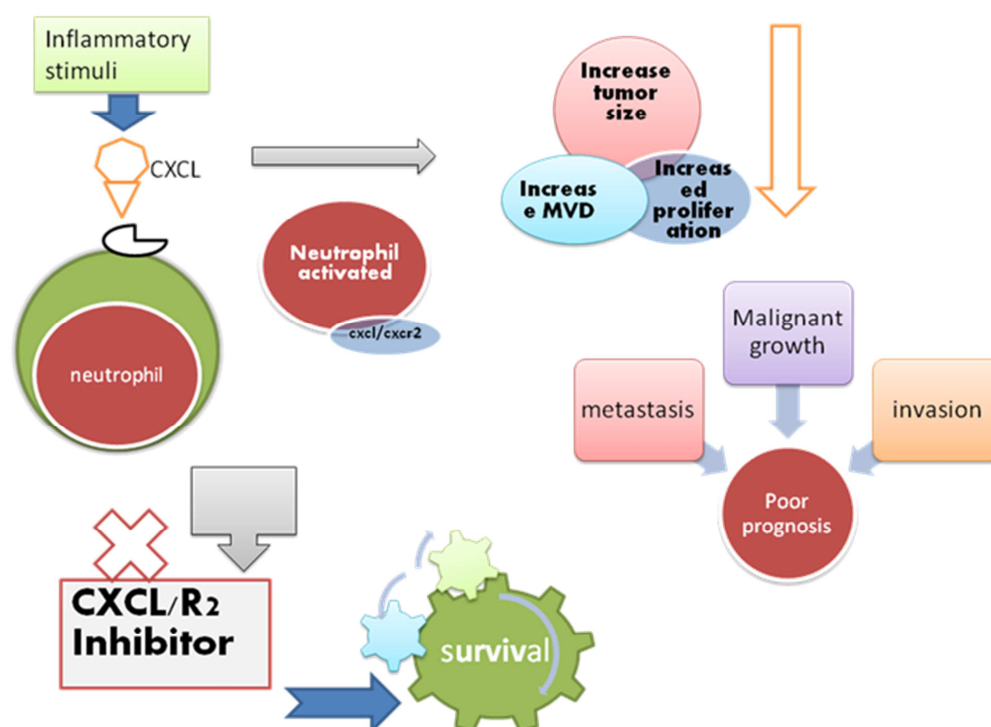
The role of macrophages in tumorigenesis is complex because there are indications that they can both prevent and promote tumor development. Tumor-associated macrophages are one of the major constituents of tumor stroma in many solid tumors and there is compelling preclinical and clinical evidence that macrophages promote cancer initiation and malignant progression (Dun et al.,

2013). Recently, Dun and colleague (Dun et al., 2013) investigated whether macrophage distribution or its density differed among normal endometrial tissue, hyperplasia, Type I, and II endometrial adenocarcinomas. By analyzing pathologic specimens of women who underwent hysterectomy for benign disorders, endometrial hyperplasia, Type I, or Type II cancers stained with anti-CD68 antibody; the author demonstrated that type I and II endometrial carcinomas sections had significantly higher macrophage density in both epithelial and stroma compartments compared with the benign endometrium (Dun et al., 2013).

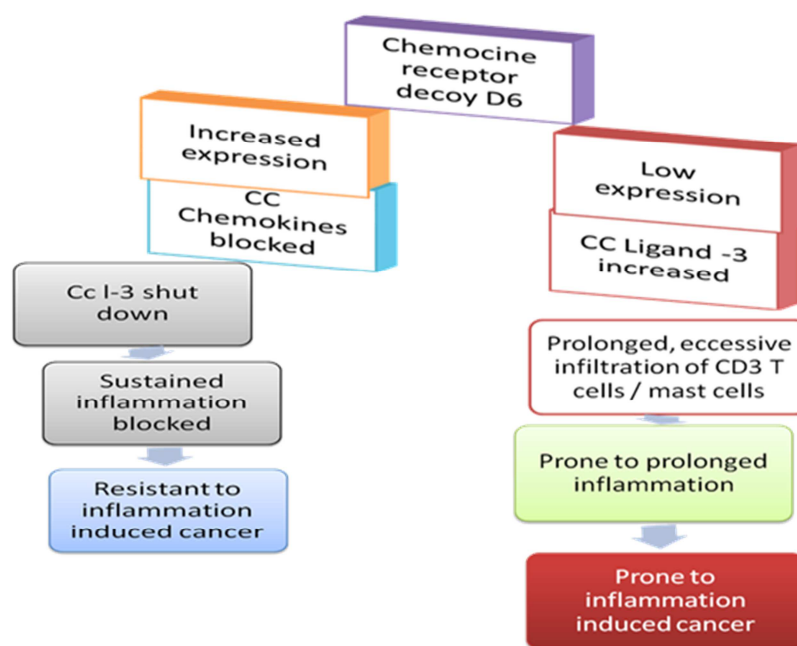
However, in that study, it was shown that in both benign and neoplastic specimens, that the numbers of macrophages were significantly higher in the stroma compared with the epithelium, surprisingly, the patients' cancer progression did not correlate significantly with the number of TAMs.

Previous report indicate that tumor-associated macrophages (TAMs) recruited to the tumor microenvironment (figure 1), play important role in the progression of cancer.

There is strong evidence for an inverse relationship between TAM density and clinical prognosis in solid tumors of the breast, prostate, ovary, and cervix, but not endometrial cancer (Dun et al., 2013).



**Figure 2:** illustrating how neutrophils recruitment into tumor contributes to aggressive malignant cancer behavior and to prognostic index. Cancer cells expressing increased level of CXCL1 or CXCR2 acquire more malignant potential and ability to migrate to distant organs; this suggests that by inhibiting the CXCL1 or CXCR2 receptors, cancer invasive characteristics may be abrogated; this may result in improved survival index.



**Figure 3:** showing the consequences of chemokine receptor decoy D6 expression and the risk of developing or being protected from inflammation mediated cancer.

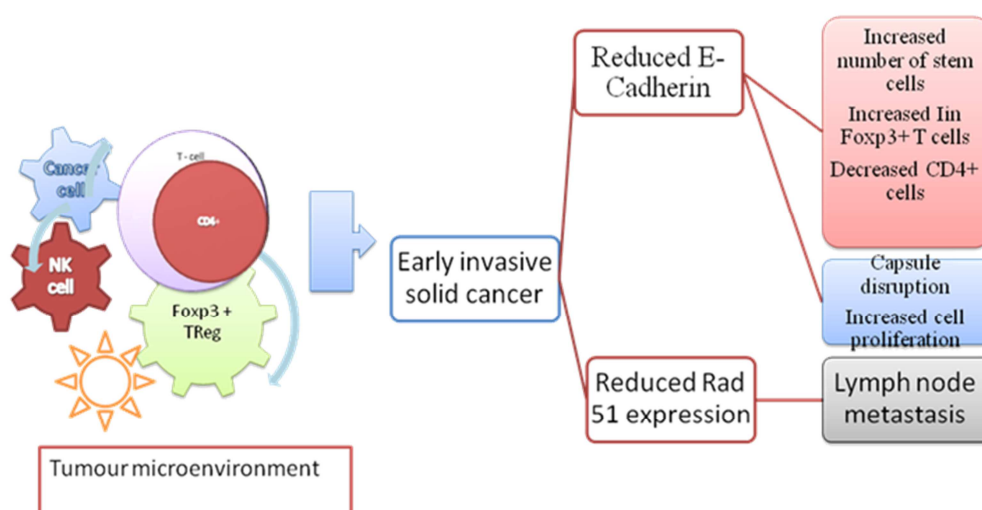
### 5.3. Nutrition, inflammation and cancer

The report of Nelson and colleagues (Nelson et al., 2003) had shown that heterocyclic amines for example, amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) contained in roasted meat or fish may contribute to prostate carcinogenesis. Also rats exposed to this product through their diet developed intestine, mammary, and prostate cancer (Sugimura et al., 2004). A 12 weeks exposure of PhIP also resulted in increased mast cell and macrophage infiltration, epithelial atrophy of the ventral lobe, followed by prostatic intraepithelial neoplasm (PIN) in rats (De Marzo et al., 2007). Borowsky *et al* (Borowsky et al., 2006) used rat as a model of human prostate cancer and studied the mechanism of prostate cancer development following exposure to PhIP. This study strongly demonstrates that the pathogenesis of prostatic neoplasia following exposure with this product occurred through inflammation and post-inflammation proliferative atrophy.

### 5.4. Cytokines and carcinogenesis

Chemokines are multifunctional secreted peptides that play an important role in regulating leukocyte migration. They are divided into 4 subgroups (CC, CXC, CX3C, and XC) according to a characteristic cysteine motif. The atypical chemokine receptor D6 is a decoy and scavenger receptor for most inflammatory CC chemokines (Aoi et al., 2011). In fact, the appropriate control of the chemokine system involves several chemokine decoy receptors, with distinct specificity and tissue distribution, defined as nonactivating chemokine

receptors able to bind the ligands and target them to degradation. The best-characterized representative of these receptors is D6, which is located on lymphatic endothelium and controls most inflammatory CC chemokines (Aoi et al., 2011). In health, the D6, has been shown to abrogate CC chemokines which is known to mediate inflammatory response; by this shut off inflammation by making the chemokines unavailable (Aoi et al., 2011; Nibbs et al., 2007) (see figure 3). CC chemokines are known to act through CC chemokine receptors (CCRs) 1 to 5, and contributes in modulating inflammatory responses (figure 3); this response is destroyed by chemokine D6 (Aoi et al., 2011). This phenomenon is critical for effective resolution of inflammation in vivo (Nibbs et al., 2007). For example, evidence from experimental studies demonstrated that mice deficient of D6 had increased susceptibility to developing cancer induced by the inflammation-producing carcinogen, the phorbol ester (Nibbs et al., 2007). In contrast, transgenic mice with lots of D6 are resistant to tumor formation (Nibbs et al., 2007). Lack of the D6 receptors which shuts down inflammatory response from CC chemokine ligand-3 (CCL3) attracts aberrantly (in excess and for a longer time) CD3+ T cells and mast cell (figure 3). This strongly suggests that. Inflammation can be protumorigenic (figure 3). In fact the molecular mechanism by which inflammatory response might result in tumorigenesis has been reviewed extensively in a previous report by the current author (Omabe and Ezeani, 2011).



**Figure 4:** showing how infiltration of tumor with particular phenotypes of the leukocytes including Foxp3+ Treg cells, CD4 + cells and mast cells may contribute in predicting tumor invasiveness and metastasis.

### 5.5. Inflammation promotes invasion and metastasis

Abundant published evidence suggests that tumor progression is not only directed by genetic changes intrinsic to cancer cells (Omabe and Ezeani, 2011). We have previously reported that there is both molecular basis for cancer initiation and progression (Omabe and Ezeani, 2011; Omabe et al., 2012; Omabe and Okorochoa, 2011). In fact our previous report suggests an important role for environmental factors including inflammation for carcinogenesis. Previous paragraphs has deciphered molecular basis of innate signaling in health and its association in inflammation. In addition, sufficient evidence linking inflammation and cancer have been presented in different forms of cancer. In a study involving 250 primary breast and prostate tumors, in which the primary immune cell especially the cytotoxic T-lymphocytes (CTL), Natural killer cells (NK) and Mast cells were analyzed by immunohistochemistry, fluorescent labeling and apoptosis assay, to assess the effects of physical disruption of the forenamed immune cells and potential impact on the epithelial capsule of human breast and prostate tumors. It was shown that at the early stage of tumor invasion, CTL, NK and Mast cells were the main types of tumor infiltrating immune cells involved in focal degenerative products of tumor capsules (Jiang et al., 2013; Yuan et al., 2013). In these two independent studies, luminal cells overlying focally disrupted basal cell layers had a substantially increased proliferation rate and elevated expression of stem cell markers compared to their adjacent morphologically similar counterparts that overlie a non-disrupted capsule (Yuan et al., 2013), suggesting that these inflammatory cells may contribute to aggressive and invasive tumor progression. The primary function of these

infiltrating leukocytes was associated with focal disruptions of the tumor capsule, which selectively favor tumor stem cells proliferation, invasion and metastasis (Jiang et al., 2013; Yuan et al., 2013). The CD4 (+) T cells, CD8 (+) T cells, and forkhead box P3-positive (Foxp3) regulatory T cells (Tregs) are the keys cells involved in immune surveillance and tolerance, respectively. The effects of the complex interaction between these cell types and the clinical outcome are not clearly understood. A most recent study found significant correlations between increased immunosensitivity for Foxp3(+) Treg/CD4(+) T-cell ratio and lymph node metastasis (figure 4) and Ki-67 ( $P=0.003$ ) and triple-negative breast cancer ( $P=0.004$ ) (Kim et al., 2011). This suggests that the increased number of Foxp3 (+) Tregs was significantly associated with lymph node metastasis and increased cell proliferation (Kim et al., 2013) (see figure 4). Of note, in the study was that lower Foxp3 (+) Treg/CD4 (+) T-cell ratio was significantly associated with triple negative breast cancer.

### 5.6. The central role of NF- $\kappa$ B and IKK activation and carcinogenesis

NF- $\kappa$ B is responsible for the transcription of the genes encoding many pro-inflammatory cytokines and chemokines. The pathway from pathogen recognition to pro-inflammatory cytokine production demonstrates a particular reliance on NF- $\kappa$ B. A role for NF- $\kappa$ B in cancer is supported from numerous reports showing that NF- $\kappa$ B is activated (i.e., nuclear) in a number of tumors. NF- $\kappa$ B activation has been reported in cancer including hematological malignancies. Nuclear factor kappa B (NF- $\kappa$ B) is as a transcription factor present in the nucleus of B cells that bound to the enhancer of the  $\kappa$  light chain of immunoglobulins (Ghosh and Karin, 2002). NF- $\kappa$ B stimulates the expression of a panel of antiapoptotic gene products including

FLICE inhibitory protein (FLIP), cIAP, survivin, B-cell leukemia/lymphoma 2 (Bcl-2), and Bcl-X<sub>L</sub>, underscoring its importance on cell death in hematologic malignancies. Once activated, NF- $\kappa$ B dissociates into NF and  $\kappa$ B, allowing NF to translocate to the nucleus; this activates more than 200 specific genes involved in cell survival, apoptosis, and active immunity. It is clear that NF- $\kappa$ B is directly involved in both cellular responses that culminate in production of cytokines and inflammation. We have previously shown that inflammation might be one of the several ways responsible for cancer initiation and progression in prostate gland (Omabe and Ezeani, 2011). In particular, inflammatory breast cancer (IBC) is the most aggressive form of locally advanced breast cancer with a high metastatic potential. At the molecular level, microarray and qPCR analysis have revealed an 'NF- $\kappa$ B signature' in IBC (Lerebours, 2008). Interestingly, the first piece of evidence implicating IKK in tumor development was in breast cancer. IKK was found to be constitutively expressed in two-thirds of the human breast cancer tissues analyzed, as well as in several human breast cancer cell lines (Lerebours, 2008).

## 6. Inflammation and cancer suppression

### 6.1. Immunosurveillance, immunoediting and cancer

By treating mouse with [7, 12-dimethylbenz[*a*]anthracene (DMBA)/12-*O*-tetradecanoylphorbol 13-acetate (TPA)], a mouse model of carcinogenesis (skin papilloma) with proinflammatory processes is created experimentally (Rakoff-Nahoum and Medzhitov, 2007; Swann et al., 2008). The [3'-methylcholanthrene (MCA)] is a different chemical for inducing fibrosarcoma model which is used to illustrate innate and adaptive immune surveillance of cancer and for investigating the existence of cancer immunoediting process (Rakoff-Nahoum and Medzhitov, 2007; Swann et al., 2008). To show that immunoediting exists to protect one from tumorigenesis, Swann and colleagues (Swann et al., 2008) exposed mice to a combination of DMBA and proinflammatory TPA stimuli; the author showed that mice lacking MyD88 (which acts downstream following TLR activation) formed fewer tumors than genetically matched inbred WT C57BL/6 (WT) controls treated in a similar manner, indicating that inflammation-mediated carcinogenesis was repressed due to lack of MyD88 molecule (Swann et al., 2008). However evidence from investigations in that study also revealed that MyD88<sup>-/-</sup> mice also formed fewer tumors than WT controls when exposed to MCA, indicating that the process of immunoediting operates to repress tumor formation. That study also demonstrated the

coexistence of inflammation-dependent tumor induction by MyD88, as well as the occurrence of the process of cancer immunosurveillance/immunoediting, known to be driven by cytokines known to be regulated by MyD88 (TNF $\alpha$  and IFN- $\alpha/\beta$ ) in the same animal (Pagès et al., 2005). Immunoediting is therefore the process by which innate and adaptive immunity work together to eliminate primary chemically induced or spontaneous tumors or to promote tumor outgrowth by mechanisms involving the dampening of tumor immunogenicity or attenuation of the protective antitumor response (Rakoff-Nahoum and Medzhitov, 2007; Swann et al., 2008). Together, the dual host-protective and tumor-promoting actions of immunity are referred to as cancer immunoediting and comprised of three distinct phases: elimination, equilibrium, and escape.

### 6.2. Tumor T memory cell, immunoediting and clinical outcome

Cancer immunoediting involves principally the lymphocytes of the adaptive immune system, with the physiologic function of protecting the host from the development of cancer and altering tumor progression by driving the outgrowth of tumor cells with decreased sensitivity to immune attack. The elimination phase of cancer immunoediting is not clearly understood, however there are indications that this process might be a continuous process which could be critical for cancer progression and survival indices. From general understanding of basic immunology, it is a common knowledge that T cells differentiate into type 1 or type 2 helper T cells (Th1 and Th2, respectively) after the expression of T-BET (T-box transcription factor 21) or GATA-3, respectively. Protective immune responses are mediated by effector memory T cells subpopulation with CD8<sup>+</sup>, CD45RO<sup>+</sup>, CCR7<sup>-</sup> (negative for CC chemokine receptor 7), CD62L<sup>-</sup> (negative for CD62 ligand), perforin<sup>+</sup>, granzyme B<sup>+</sup> phenotypes. Stimulation with an antigen induces these cells to exert an immediate effector function by releasing cytotoxic mediators. In a clinical study, Pages *et al* (Pagès et al., 2005) demonstrated that infiltration with leukocytes including the T cell memory was associated with cancer survival. In particular, data from the analysis of 39 colorectal cancers cases showed that presence of effector memory T cells within the tumor, defined by the presence of CD3, CD8, CD45RO, CCR7, CD28, and CD27 markers, was associated with absence of tumor metastasis which correlated with a good clinical outcome (Pagès et al., 2005). This means T memory subpopulations may be involved in the process of immunoediting which tends to repress tumor progression.

In a separate study, Camus *et al.* also demonstrated that co expression of genes mediating cytotoxicity and Th1 adaptive immune responses accurately



predicted patient survival independently of the metastatic status (Camus et al., 2009). The Author observed significant positive correlations between markers of innate immune cells [tumor-associated macrophages, dendritic cells, natural killer (NK) cells, and NK cells]. There is no full explanation yet for involvement of NK and dendritic cells in immunoediting. A related study also showed that decreased number of CD8 (+) T cells was significantly associated with tumors with lymph node metastasis ( $P=0.027$ ), higher stage (stage III,  $P=0.013$ ), and immunopositivity of Ki-67 ( $P=0.026$ ) (Kim et al., 2013).

Put together, these suggest that efficient coordination of the intratumoral immune response may predict a favorable outcome in solid cancers. It appears that recognition of tumor-specific antigens by lymphocytes may be involved in the process of immunoediting against cancer cells.

Put together, current data suggest that infiltration of tumor T memory effector cells especially those with gene expression profile for granzymes activity, perforin, and granulysin which are known to have higher capacity for releasing cytotoxic compounds may be associated with good clinical outcome in patients with colorectal cancer. Available data from literature suggest that leukocytes of the particular phenotypes are seriously involved in immunoediting.

### **6.3. High CD8+/Foxp3 ratio and presence of CD45R0+ T lymphocytes predicts better overall survival**

As discussed above, the presence of tumor-infiltrating lymphocytes (TIL) may be of prognostic importance in a variety of malignancies. A recent study determined the prognostic value of CD8 (+) cytotoxic T-lymphocytes (CTL), FoxP3 (+) regulatory T-lymphocytes (Treg) and CD45R0 (+) memory T-lymphocytes in endometrial cancer. The author found that high numbers of intra-tumoral CD8(+) T-lymphocytes and the presence of CD45R0(+) T-lymphocytes were all strongly associated with well-known favorable prognostic factors in endometrial cancer (de Jong et al., 2009). Furthermore, high numbers of CD8(+) T-lymphocytes and a high CD8(+)/FoxP3(+) ratio were associated with a better disease free survival (DFS), and high numbers of CD8(+) T-lymphocytes plus the presence of CD45R0(+) T-lymphocytes were associated with a prolonged overall survival (OS) (de Jong et al., 2009).

Clearly, that study showed that the presence of TIL was an independent prognostic factor in endometrial cancer and suggests that some infiltrated cells may play important role in immunoediting and cancer prevention in endometrial cancer.

### **6.4. Role of granzymes and cancer**

Cytotoxic T cells (CTL) and natural killer (NK) cells recognize and kill virus-infected or transformed cells through two major pathways: either through introduction of a battery of proteases to the target cell cytosol; these proteases are called granzymes, or through TNF superfamily-dependent killing (Lopez et al., 2013).

Granzymes are a family of functionally diverse and structurally related serine proteases that differ markedly in their substrate specificities which have been traditionally believed to be cytotoxic in nature and stored, along with the pore-forming protein perforin in the granules of cytotoxic lymphocytes and natural killer cells (Lopez et al., 2013). Although they were discovered over two decades ago, there remain many unanswered questions as to the precise roles of granzymes in physiology and pathology.

To date, there are 5 human granzymes (A, B, H, K, M) which are thought to be involved in ensuring efficient immune-mediated killing of unwanted cells that could otherwise be resistant to the proteolytic activity of a single granzyme (Lopez et al., 2013; Bian et al., 2013). The pore-forming protein perforin is critical for the delivery of granzymes into target cells before a cell death could be triggered (Bian et al., 2013).

Elevated levels of circulating extracellular granzymes A and B have been linked with various inflammatory conditions and diseases (Bian et al., 2013). When activated cells recognizes a target, cytotoxic granules within the cytoplasm move along microtubules to polarize at the plasma membrane, adjacent to the target, where they are secreted into the immunological synapse between the two cells (Lopez et al., 2013).

Although a large body of evidence implicates cytotoxic granule constituents in pathways resulting in target cell death, recent evidence suggests that these granzymes may also serve alternative functions as initiators or amplifiers of inflammatory responses.

### **6.5. Granzymes mediate immunoediting**

There are abundant reported cases that support involvement of granzymes and perforins in efficient immunoediting. Example, evidence from experimental studies have shown that mice deficient of either perforin or granzymes developed spontaneous tumor (Smyth et al., 2000; Shankaran et al., 2001). Mice with lack of granzymes also developed spontaneous tumor while more than half of mice deficient of perforin also developed tumor quicker when exposed to carcinogens (Smyth et al., 2000; Shankaran et al., 2001). These evidences therefore strongly suggest that granzymes and perforins may have a central role in immunoediting.

## 7. Inflammations as a chemotherapeutic molecular target for treatment and monitoring

### 7.1. Targeting inflammatory markers for cancer treatments and prevention

Studies reporting reduced cancer incidence in patients undergoing treatment with anti-inflammatory drugs provided the most convincing evidence for a role of inflammation (Omabe and Ezeani, 2011), this is because anti-inflammatory compounds inhibit cyclooxygenase-2 (Cox-2) activity, since this enzyme is the primary target for prevention of inflammation (Tabriz et al., 2013). For example, in transitional cell carcinoma (TCC), cyclooxygenase (COX)-2 has been reported as an attractive therapeutic target. A cross-sectional study involving ninety-two paraffin embedded blocks, which were selected from patients with urinary bladder TCC who underwent cystectomy or transurethral resection (TUR), evaluated the expression of COX-2 and its association with several clinicopathological characteristics of the tumor, showed that COX-2 was expressed in 50 % of the patients investigated (Tabriz et al., 2013). It was also found that COX-2 was markedly expressed in high grade bladder TCC (62.1%) versus other grades and that there was statistically significant difference in COX-2 expression between various grades ( $p=0.008$ ) (Tabriz et al., 2013). In addition, lymphatic and perineurial invasion were associated with the expression of COX-2 ( $p=0.001$ , 0.015 and 0.039, respectively) (Tabriz et al., 2013). However, other parameters such as stage, tumor size, venous invasion and lymph node metastasis did not show any significant relationship with this marker (Tabriz et al., 2013). That study strongly suggests that the inflammatory marker, COX-2 was expressed in urinary bladder TCC especially in high grade forms, indicating that inflammation may have a probable role in the differentiation of this tumor.

From the available reports, there are reasons to suggest that COX-2 might be a valuable biological target molecule (see figure 5) in the evaluation and treatment of patients with bladder TCC, since high grade cancers show increased level of this inflammatory marker. It follows therefore that inhibition of inflammation may abrogate cancer development (figure 5). In addition, by treating mice with a combination of 2% dextran sulfate sodium (DSS) and azoxymethane (AOM), colon cancer was induced with profound production of inflammatory cytokines, i.e., interleukin-12 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ); however, whenever the mice were treated with 4-vinyl-2,6-

dimethoxyphenol (canolol), a potent anti-inflammation agent obtained from crude canola oil, those mice developed a reduced occurrence of cancer, to 60%, compared with control mice, 100% of which had colon cancer (Fang et al., 2013). In that study, the numbers of tumors in each mouse were also significantly reduced in mice that received the canolol-containing diet ( $5.6 \pm 2.0$ ) compared with AOM/DSS control mice ( $10.8 \pm 4.2$ ). Moreover, inflammatory cytokines (i.e., COX-2, inducible nitric oxide synthase, TNF- $\alpha$ ) and oxidative responding molecules, i.e., heme oxygenase-1 in colon were all suppressed during this treatment with the anti-inflammatory compound canolol (Fang et al., 2013). These studies strongly show that by targeting key inflammatory markers in the tumor microenvironment, neoplastic development, progression and metastasis would be controlled (figure 5).

Furthermore, we have recently shown that the tumor microenvironment was associated with substantial features of inflammatory marker including hypoxia and oncogenic activities (Omabe and Onyekachi, 2013) (figure 1). Another preclinical study that involved combining dosage of celecoxib (a known cox-2 inhibitor) and a dietary fats, n-3 polyunsaturated fatty acids (PUFA) often found in fish oil (which exerts cancer chemo preventive effect mediated through COX-2 inhibition); revealed that pretreatment of carcinogen-treated animals with celecoxib and/or fish oil altered inflammation mediated redox signaling with reduced c-myc, p53 expression, apoptosis, and proliferation in breast cancer model (Negi et al., 2013). However, a combination dosage of celecoxib and fish oil treatment in that study resulted in better chemo preventive effect in the female Wistar rats (Negi et al., 2013). The results suggest that a combination of celecoxib and fish oil which provide better anti-inflammatory synergy would be more effective in the chemoprevention of experimental mammary carcinogenesis, and this effect can be attributed to the modification of redox signaling. However, a large historical cohort study found no evidence of an association between non-aspirin non steroidal anti-inflammatory drug (NSAID) or aspirin use and cervical cancer risk (Wilson et al., 2013). Put together, there are strong evidence to suggest that inflammation, (marked with COX-2 expression) may mediate carcinogenesis in both animal and clinical models (figure 2 and 3), and that anti-inflammatory agents may abrogate cancer development (figure 5) and improve disease free survival among cancer patients (figure 1-4).

Agent	Target	Cancer type	Phase of clinical trial	Route of administration
AS15	TLR2,4 and 9	NSCLC	II	I.M
BCG	TLR 2 and 4	Melanoma	III	I.T
CBLB502	TLR5	HNSCC	I	s.c
GNKG168	TLR9	ALL, AML	I	I.V
Imiquimod	TLR7	Anal dysplasia	IV	Local
Hiltonol	TLR3	ALL, MDS, Melanoma, Solid tumor	I, II	s.c
ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; HNSCC, Head and neck squamous cell carcinoma; MDS, Myelodysplastic syndrome; NSCLC, Non small cell lung carcinoma;				

**Table 2:** Recent clinical biological agents in clinical trials targeting inflammatory molecules for cancer treatment, adapted and modified from Vacchelli et al., 2013.

Furthermore, the role of TLR molecules in NF- $\kappa$ B activation and proinflammatory chemokine production and their participation in cancer development and progression have been discussed (table 1 and figure 1-4).

Emerging data show that this family of pattern recognition receptors has been attributed a critical role in the elicitation of anticancer immune responses; in response to this, some immunochemotherapeutic regimens based on natural or synthetic TLR agonists have been developed, some of which are in several stages of clinical trials, (table 2).

It is hoped that in the near future, more inflammatory based therapies either biological (table 2) of chemical compounds (figure 5) would be developed for cancer treatment.

In conclusion, there are sufficient convincing data that suggest that inflammation induces and promotes cancer.

The current work provides new algorithms to clarify different ways inflammation may result in carcinogenesis and cancer control; this allows scientists, new and old and clinicians involved in cancer management to have a concise

understanding of some emerging issues in oncoimmunotherapy.

In addition, various new facets and molecular target onto which diagnosis, treatment and monitoring and drug design may be focused have been discussed. The understanding of the complex nature of immunoediting which is an emerging concept in oncoimmunology may evolve to yet a new horizon in cancer research and management.

Importantly, some drugs are currently being designed (table 2) to target a number of both biological and biochemical markers (table 1) involved in spearheading inflammation dependent cancer progression.

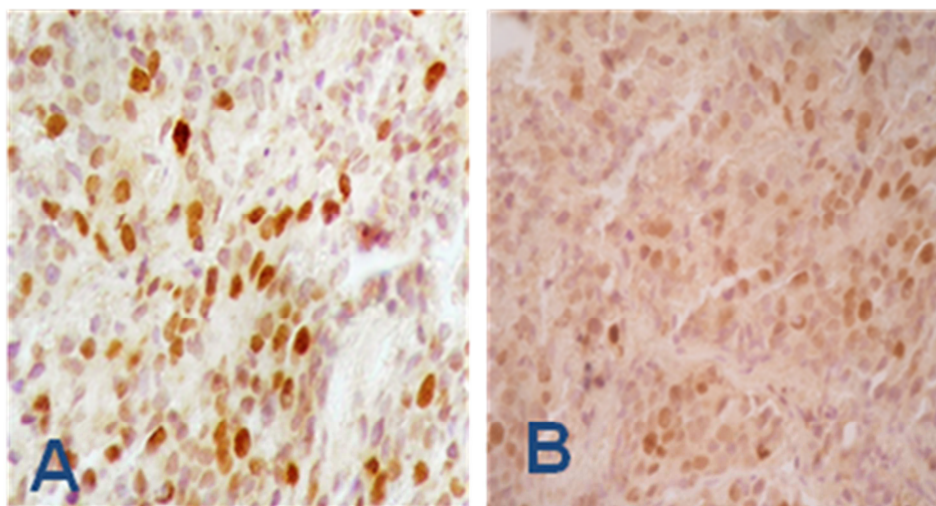
Sufficient data indicate that availability and accessibility of various anti-inflammatory agents would contribute much to cancer prevention.

#### **Submission declaration:**

The authors declare that no part of this work has been published elsewhere or is awaiting publication anywhere.

I declare no conflict of interest, and that no fund from any funding body or the University was made available for this work.

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**Figure 5:** showing immunohistochemical co-localisation of ki-67 in xenograft tumours. A shows control tumour without anti-inflammatory treatment, with increased expression of Ki-67, indicating malignant cancer progression. B shows reduction of ki-67 expression after treatment with Cox -2 inhibitor, indicating reduced cancer progression and tumour control. Produced from the Laboratory of Dr. Maxwell Omabe.

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